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Air pollution in early life and adult mortality from chronic rheumatic heart disease.

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Abstract

Background: Chronic Rheumatic Heart disease (RHD) remains a globally important cause of heart disease. The reasons for the continuing high prevalence of this disease are obscure but it may have its origins in the poor social and economic conditions with which the disease has been consistently and strongly linked. Mortality studies from the UK have suggested the importance of adverse environmental factors in early life; these studies demonstrated specific geographical associations between high rates of chest infection during infancy and subsequent RHD. They also raised the possibility that early air pollution, which is known to be strongly linked with chest infection during infancy, may predispose to RHD.

Methods: We related estimates of air pollution and social conditions developed by Daly in 1951-2 for 83 UK urban areas to their subsequent RHD mortality rates at ages 35-74 in men and women during 1993-2012.

Findings: There were strong relationships between domestic air pollution and RHD (relative risk per SD increase in pollution 1·168, 95% CI: 1·128 to 1·210, $p < 0.001$). Inclusion of published data on social class, education, crowding and population density in multiple regression analyses showed that the air pollution associations were independent of these; only the effect of overcrowding remained statistically significant in combination.

Interpretation: We present the first evidence of an association between air pollution in early life and RHD. Although there are several limitations to this study, the strength and consistency of the results, together with their biological plausibility, suggest a causal link. This deserves attention because it may have important consequences for the control of RHD in resource-poor countries where widespread use of biomass fuels and consequent pollution remain a problem.

Funding: None

Introduction

Chronic rheumatic heart disease (RHD) is the long-term consequence of a systemic, inflammatory, autoimmune response initiated by infection with Lancefield group A, β -haemolytic streptococci, *Streptococcus pyogenes*. While the organism is widespread and the commonest cause of bacterial pharyngitis in children, accounting for 20 to 30% of cases,¹ it is still not known why only a small proportion of those infected develop this unusual response.² RHD has virtually disappeared in the West but remains an important public health problem in many resource-poor countries. It is one of the commonest causes of heart disease in sub-Saharan Africa, is widespread in the Middle East and Asia, and is also found in the poor indigenous populations of some wealthy countries.³⁻⁵ The disease has been consistently and strongly linked to poor living conditions, both historically in the UK and US, and currently in countries where the disease remains endemic.⁶⁻⁸

Epidemiological studies in resource-poor countries present many challenges that are difficult to overcome. Therefore, we have used historical data from the UK to investigate the aetiology of RHD. These data suggested the importance of adverse environmental factors in early life.⁹ They showed that areas of England and Wales with high infant mortality rates early in the 20th century were the same areas with high mortality rates from RHD some 50 to 60 years later. The associations were strong and specific to the post-neonatal period, suggesting a dominant influence of external environmental factors in infancy or early childhood on subsequent occurrence of RHD rather than maternal factors, which would have tended to increase neonatal mortality. Analyses of the specific causes of infant death showed that the strongest predictor of RHD was mortality from bronchitis and pneumonia. These findings suggested two possibilities. Firstly, early respiratory infection might predispose to the development of RHD,

which could occur, for example, by molecular mimicry with invading pathogens initiating the autoimmune response.¹⁰ Secondly, both conditions could be linked through a common environmental risk factor. Risk factors known to influence susceptibility to respiratory tract infections in young children include low birthweight, low rates of breastfeeding, overcrowding and exposure to air pollution.^{11, 12} In contrast, little is known about the risk factors for infection with group A streptococci, except that it is spread by overcrowding and close person to person contact with infected nasopharyngeal or oropharyngeal secretions.^{6, 13} Our previous analyses, however, suggested that overcrowding *per se* could not explain the strong geographic associations between respiratory infection and RHD.⁹ Of the remaining possible risk factors, air pollution is the strongest and most consistently linked with lower respiratory tract infections in young children.¹⁴ Several meta-analyses have examined the evidence concluding that both indoor^{15, 16} and outdoor¹⁷ pollution are associated with increased morbidity and mortality from respiratory tract infections.¹⁷ Although there are no prior data linking air pollution with RHD, this possibility is encouraged by the known adverse effects of smoke on immune function and the mucosal barrier, which could be important in streptococcal infection.¹⁸ It could also account for the links between RHD and poverty, as pollution and poor air quality are strongly associated with living conditions, particularly in resource-poor countries where biomass combustion and its resulting pollution are common.¹⁹

Our aim in this study was to test whether air pollution in early life is linked with subsequent RHD. We used indices of domestic and industrial pollution based on fuel consumption in 1951-52 that were developed by Daly for each of 83 major urban areas in the UK, along with concurrent measurements of socioeconomic conditions.²⁰ These were compared with subsequent mortality data from RHD in the same geographical areas.

Method

Data sources

In the years following the Second World War, coal and other forms of fuel were rationed and distributed under the control of local fuel overseers (LFOs). Data on the quantities of different types of fuel burnt annually in each of 1330 LFO areas between May 1951 and May 1952 were published by the Ministry of Fuel and Power.²¹ Domestic fuels were house coal, coke, anthracite, and boiler fuel, while industrial fuels were smokeless solid fuel, other solid fuel and liquid fuels (gas/diesel oil, fuel oil, and creosote/pitch mixtures). Daly published these consumption data for 83 county boroughs refined by calculating consumption figures adjusted for the density of housing in each borough to provide an estimate of tons of smoke per annum per acre of built-up area.²⁰

The Office of National Statistics (ONS) provided extracts from all death certificates in England and Wales during 1993 to 2012, the period covered by the ninth and tenth revision of the ICD. The ICD codes used to define causes of death are given in the tables. Mortality rates were calculated using population estimates provided by ONS for each local authority area. The main technical problem was to relate the 1952 county boroughs to the current local authority areas, following successive local government reorganisations in 1974, in the 1990s, and 2009. The areas were unchanged in 35 of these, the new local authority area had increased from the pre-1974 boundaries in 38 and the county boroughs had merged for 10 areas. For the latter, the pollution and socioeconomic data were averaged, giving a total of 78 local authority areas. The Registrar General's Statistical Review for 1951 also provided data on infant mortality.²² The data were divided into neonatal mortality (deaths during the first month of life) and post-

neonatal mortality (deaths from one month to one year) Numbers of infant deaths according to specific causes were also classified using the World Health Organization's 6th revision of the International Classification of Disease (ICD). These were grouped according to an abridged list of 36 causes adopted by the Registrar General and the Ministry of Health.

Confounding

Historically air pollution was worse in predominantly industrial towns with a high population density; these towns also tended to have large populations of factory workers who left school early and worked in low status occupations.²⁰ These are important potential confounders in a study of air pollution and RHD as poverty and overcrowding are known to facilitate the spread of the causative streptococcal agent responsible for RHD. Daly's published data for the 83 county boroughs provided indices of social class, based on a weighted average of the proportions of each of five social classes within each borough; overcrowding, assessed by proportion of households with more than one person per room; density, the number of people per acre; and educational achievement, the proportion of employed men in each borough who left school before the age of 15 years for each of the county boroughs. These four variables were used to control for confounding in the analysis.

Statistical methods

We studied deaths in people aged between 35 and 74 years, as this was the approximate age range of the generation who were infants or young children in 1951-52 and excludes deaths in older age groups where the cause is less likely to have been ascertained accurately. We calculated the number of deaths expected in each area in five-year age groups, according to sex, by multiplying the population size by the national death rate. We calculated the standardised mortality ratio (SMR) as the percentage of observed to expected deaths, such that the overall national SMR is 100%. We used Poisson regression to model SMRs. This weights

the analysis appropriately to allow for variation in population size across local authority areas.

We used a Fisher-Yates transform to express the pollution and socioeconomic and infant mortality rates in standardised form. This ensures that they have means of zero, unit standard deviation and a symmetrical distribution, so that the results can be compared directly. The

interrelationships of the variables were examined in a conditional independence analysis which shows the partial correlation coefficients between variables after controlling for all other variables.²³

Results

A total of 3,939 deaths (1,330 men and 2,609 women) from chronic RHD were recorded at ages 35-74 in the 78 local authority areas between 1993 and 2012. The combined 1993 population in these areas was 8.0 million (3.9 million men and 4.1 million women) and the overall annual death rate was 24.6 per million (17.1 per million in men and 31.8 per million in women). The overall SMR in the 78 areas was 117.1 and varied from 40.4 in Great Yarmouth to 207.5 in Merthyr Tydfil. Table 1 shows the infant mortality rates and mortality rates in the neonatal and post-neonatal periods, together with the major causes of infant death from the 1951 registrar general report, according to the abridged list.²² The table also shows the measures of pollution derived from Daly's data together with demographic variables.²⁰

Table 2 shows associations between RHD mortality and measurements of pollution and socioeconomic variables. The strongest relationships were with domestic pollution and overcrowding (also shown in Figure 1), although there were significant associations with all the variables in Table 2 except power station emissions. A further multivariate analysis with all the variables included showed that only the effects of domestic pollution and overcrowding remained statistically significant. Table 3 illustrates how domestic pollution and overcrowding are associated with SMRs for RHD in the 78 local authority areas. At any level of crowding,

increasing domestic air pollution is associated with increased risk and at any level of air pollution, overcrowding increases the risk. There was no evidence of an interaction between the effects of pollution and crowding. The effects of the potential confounders were tested singly and in combination. There was no evidence of non-linear relationships. We also examined the effect of changing the age groups studied and found similar relationships in each age group although, as expected, the associations were weaker in the older age groups where death certification was less likely to be accurate. A sensitivity analysis suggested that an unknown variable would have to correlate very strongly ($r > 0.5$) with both domestic air pollution and rheumatic heart disease to confound the relationships we have observed. Figure 2 shows the results of the conditional independence analysis which shows that RHD mortality is associated with both air pollution and household overcrowding after controlling for all other variables. The effects of domestic pollution were stronger in women than in men, adjusted relative risk (RR) 1.161 (1.087 to 1.241) vs. 1.04 (0.948 to 1.140).

Table 4 shows the relationship between RHD and measures of infant mortality from 1951. In univariate analyses, there was a strong association with infant mortality. This was due to an association with post-neonatal mortality but not with neonatal mortality. Within the causes of post-neonatal mortality there were strong associations with pneumonia, bronchitis, and gastritis, enteritis, and diarrhoea. However, when these variables were combined with domestic air pollution and household overcrowding in a multivariate analysis (Table 4), only the effect of air pollution and crowding remained statistically significant.

Table 5 compares the effect of domestic air pollution on RHD with other causes of mortality. The effect of pollution on bronchitis was strongest but the effect on RHD was in turn much stronger than the effects on ischaemic heart disease, cerebrovascular disease or cancer.

Discussion

We have shown a strong geographical correlation between current adult mortality from chronic RHD and exposure to domestic pollution in infancy (Figure 1 and Table 2). These analyses were based on adult mortality over 20 years in men and women aged 35 to 74, living in 78 local authority areas, and which accounted for approximately a third of the population of England and Wales. The correlation was stronger in women than in men and appeared to be independent of potential confounding factors including social class, overcrowding, population density and educational level. Although it is possible that an unknown confounder could account for our finding, this is unlikely as a sensitivity analysis suggested that this would have had to correlate very strongly with both air pollution and RHD; none of the socio-economic variables we examined had these characteristics.

Our study relies upon data derived from a number of sources, collected in different time periods. For example, we used coal consumption data as an index of domestic air pollution. This approach has been validated by its extensive use in studies over the last 60 years, demonstrating correlations with many outcomes including early growth,^{24, 25} chronic bronchitis and lung cancer.^{20, 26, 27} Our own data concur with those earlier studies, showing that coal consumption strongly predicts mortality from chronic bronchitis, cardiovascular disease, and cancers (Table 5). Together, these findings suggest strongly that coal consumption is a valid index of domestic air pollution. Although the lack of direct measurements of smoke exposure in our study could be perceived as a limitation, such measurements are unlikely to be feasible or reliable for integrating smoke exposure over long periods of time. In addition, the coal consumption measures used here have been shown to correlate strongly with subsequent measurements of air pollution in the UK.²⁶

Another potential limitation is our use of mortality as an index of the prevalence of chronic RHD. Although mortality from this disease is relatively uncommon – it has been estimated that RHD is associated with a death rate of 1·5% per year³ – mortality rates have been widely used as an indicator of disease prevalence and both geographical differences and the decline in occurrence of the disease in the Western world are paralleled by the mortality data. Furthermore, certification of death from RHD has proven to be surprisingly accurate. Attribution of death to this cause is unlikely unless there is significant valve disease and it has been estimated that 61% of deaths are correctly classified.²⁸ Others have argued that geographical differences in mortality from a wide variety of causes including RHD merely reflect differences in medical care as a consequence of social class differences.²⁹ In our study, however, we had extensive data on socioeconomic factors including social class, education, crowding and population density, and our multivariate analysis (Table 2) showed clearly that the association with domestic pollution was independent of all these factors.

Our findings also confirm our previous data showing strong historical geographical correlations between infant mortality in 1911 to 1921 and subsequent RHD mortality in England and Wales between 1968 and 1978.⁹ As observed previously, the correlations were much stronger with post-neonatal mortality than neonatal mortality. Moreover, detailed information on the major causes of mortality showed that it was those local authority areas that had high mortality from bronchitis or pneumonia that also had the highest subsequent mortality from RHD. However, as shown in the multivariate analyses (Table 4), the effect of domestic pollution was much stronger than that of infant respiratory infection.

An inevitable consequence of evaluating early effects on major causes of late life mortality is the long latency between exposure (measurements of pollution in this case) and the mortality data. During this time, there have been successive changes in local authority boundaries as a result of which, there is only an approximate match between the boundaries used in the 1951

census to construct the pollution data and the current local authority boundaries. Although it might be argued that these changes, perhaps combined with migration, could obscure associations, they are very unlikely to have resulted in the strong correlations reported in Table 2 and the Figure. During the time period of this study, most migration within the UK occurred over short distances with only a small minority migrating significant distances.³⁰

The major finding of this study was a strong correlation between an index of early-life domestic pollution exposure and current mortality from chronic RHD that was independent of known possible confounding factors. Interestingly, the multivariate analysis (Table 2) showed that overcrowding was the only other factor significantly associated with RHD. Overcrowding is known to facilitate the spread of group A β -haemolytic streptococcal infection and has consistently been described as a risk factor for RHD. For example, the classical studies of disease outbreaks in military barracks during the 1950s showed that spacing of beds influenced the rates of bacterial acquisition.^{6, 31} The data in Table 2 and the Figure suggest that the effect of domestic pollution has a similar magnitude to that of overcrowding and that both combine in an additive fashion to affect the prevalence of RHD (Table 3).

It is reasonable to assume that measures of domestic fuel consumption reflect air pollution, as there is a direct relationship between amount of fuel burnt and pollution emitted. Although this relationship might vary to a limited extent according to combustion efficiency, the means of combustion are likely to have been very similar across the UK in the period that we studied. The use of coal as the major source of domestic heating in the post-war years would have exposed children to pollution, both in the home and in their local environment. Industrial pollution seemed to have no additional effect in the model in Table 2. Although the amounts of industrial fuel consumed were higher (Table 1), pollution from this source would have been vented through taller chimneys, decreasing ground-level pollution in approximate proportion to the inverse square of the chimney height.³² Thus, it may have been less likely to contribute to

the infants' exposures. While the data presented here were collected between 1951 and 1952, they are likely to reflect smoke emission over many years – domestic consumption data suggest that coal consumption in the UK was fairly constant during the late 1940s, declined a little during the 1950s and only fell dramatically after 1960.³³ Hence it is difficult from our data to determine the stage of infancy or childhood when exposure might have greatest impact on risk of developing RHD.

A typical, inefficient domestic grate in the post-war years, burning relatively low-grade, sulphurous domestic coal (economic necessity in the post-war years meant that better-quality "hard" coals tended to be exported) would have produced lots of smoke, rich in a wide variety of potentially toxic compounds. These would include compounds of sulphur, halides, and trace elements, together with complex mixtures of aliphatic and aromatic hydrocarbons; the latter including both polycyclic and heterocyclic compounds. These would affect both the home environment and the immediate neighbourhood. It is feasible that these could increase the susceptibility to β -haemolytic streptococcal infection, episodes of rheumatic fever and subsequent RHD. Smoke can affect epithelial integrity and particulate pollution is well-known to have potent immunomodulatory effects.¹⁸ Alternatively, it is possible that polycyclic hydrocarbons may chemically modify vascular collagen⁴³⁴ – which is now thought to be the target of the autoimmune response in RHD, increasing its susceptibility to autoimmune processes. Finally there is increasing suspicion that the endothelial response to autoimmune-mediated injury is an important determinant of whether there is progression to clinically evident heart disease in patients who have had rheumatic fever³⁵ and there is now substantial evidence of effects of smoke on endothelial function.³⁶ However it is also possible that air pollution may be linked with other factors in childhood which in turn predispose to rheumatic

fever. Viral infections have been suggested as possible co-factors operating via a process of molecular mimicry between viral proteins and cardiac components.¹⁰

In conclusion, we present the first evidence of an association between air pollution in early life and RHD. Although there are several limitations to this study, the strength and consistency of the results, together with their biological plausibility, suggest a causal link. This possibility deserves attention because it may have important consequences for the control of RHD in resource-poor countries where widespread use of biomass fuels and their consequent pollution remain a problem. The data suggest a need for confirmatory case-control studies to be instigated in areas with a high prevalence of RHD together with appropriate laboratory studies examining the effect of smoke on the immune response to rheumogenic streptococci. Conclusive evidence, however, is only likely to come from a smoke abatement trial which would need to be carried out in an area with continuing high domestic air pollution.

Conflict of interest: none

Authors' contributions: DP & CO analysed the data, DP, CO, MW & AJ contributed to the writing of the text.

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Table 1: Infant mortality, indices of pollution and demographic variables in the 78 local authority areas.

	Median	Quartiles
Mortality per 1000 live births (1951)		
Infant	32.6	28.1,37.2
Neonatal	19.2	16.8,22.3
Post neonatal	12.4	10.5,15.7
Pneumonia ¹	4.3	2.9,6.0
Bronchitis ²	0.5	0,1.0
Gastritis, enteritis & diarrhoea ³	1.2	0.6,2.1
Congenital malformations ⁴	1.4	1.0,2.3
Other defined and ill-defined disease ⁵	2.0	1.0,2.8
Indices of Pollution (1951-2)		
Domestic (tons of smoke per annum per acre)	0.43	0.32,0.52
Industrial (tons of smoke per annum per acre)	0.54	0.35,0.72
Power station (see Daly ²⁰)	144.5	59.0,353.1
Demographic variables(1951-2)		
Social class score	3.27	3.21,3.37
Crowding (% households with >1 person/room)	16.4	12.8,19.9
Density (persons per acre)	45.0	36.7,55.6
Education (% leaving school aged <15yrs)	78.0	74.4,82.0

¹ICD 490-493,763;² ICD 500-502;³ ICD 543,571-2, 764; ⁴ICD 750-759 ⁵ICD 210-254,270-326,340-402,530-539,542,544-570,573-587,600-609,611-637,690-749,760-762,765-795.

Table 2: Associations between air pollution or socioeconomic factors assessed in 1951-2 and RHD mortality in men and women aged 35-74 during 1993-2012 in the 78 local authority areas.

Predictor (SD score)	Relative risk	95% Confidence interval	p-value
Univariate analyses			
Domestic air pollution	1.168	1.128 to 1.210	<0.001
Industrial air pollution	1.094	1.055 to 1.133	<0.001
Power station	1.022	0.990 to 1.054	0.18
Social Class	1.128	1.089 to 1.168	<0.001
Crowding	1.168	1.128 to 1.210	<0.001
Density	1.110	1.073 to 1.150	<0.001
Education	1.081	1.044 to 1.118	<0.001
Multivariate analysis			
Domestic air pollution	1.117	1.059 to 1.179	<0.001
Industrial air pollution	1.056	1.000 to 1.115	0.052
Power station	0.989	0.958 to 1.022	0.52
Social Class	0.993	0.934 to 1.055	0.80
Crowding	1.114	1.062 to 1.169	<0.001
Density	0.979	0.930 to 1.030	0.41
Education	0.970	0.919 to 1.023	0.27

Table 3: Standardised mortality ratios for RHD in men and women aged 35-74 during 1993-2012 according to quartiles of domestic air pollution and degree of overcrowding in 1951-2. (Number of local authority areas in parentheses)

% of House-holds with >1 person per room	Domestic air pollution (tons of smoke per acre of built-up area per annum)				
	≤0.31	-0.42	-0.52	>0.52	All
≤12.6	83(10)	108(3)	114(4)	69(1)	96(18)
-16.2	86(6)	107(6)	106(4)	147(3)	109(19)
-20.0	106(3)	126(5)	121(9)	151(5)	127(22)
>20.0	-(0)	130(5)	135(5)	150(9)	141(19)
All	87(19)	118(19)	120(22)	145(18)	117(78)

Table 4: Associations between infant mortality and RHD mortality in men and women in the 78 local authority areas.

Predictor (SD score)	Relative risk	95% confidence interval	P-value
Univariate analyses			
Infant mortality	1.061	1.027 to 1.097	<0.001
Neonatal mortality	1.003	0.971 to 1.036	0.86
Post neonatal mortality	1.081	1.047 to 1.117	<0.001
Pneumonia	1.062	1.026 to 1.100	<0.001
Bronchitis	1.085	1.047 to 1.125	<0.001
Gastritis, enteritis & diarrhoea	1.061	1.024 to 1.099	0.001
Congenital malformations	1.016	0.980 to 1.055	0.38
Other defined and ill-defined disease	1.041	1.003 to 1.081	0.033
Multivariate analysis			
Domestic air pollution	1.121	1.070 to 1.175	<0.001
Overcrowding	1.106	1.057 to 1.157	<0.001
Pneumonia	0.964	0.923 to 1.006	0.10
Bronchitis	0.997	0.956 to 1.039	0.88
Gastritis, enteritis & diarrhoea	1.016	0.977 to 1.056	0.43
Other defined and ill-defined disease	0.998	0.958 to 1.040	0.93

Table 5: Comparison of the effect of domestic air pollution in 1951-2 on RHD mortality with other causes of mortality in men and women.

Cause of mortality	Relative risk (95% CI)	Relative risk (95% CI)*
Chronic rheumatic heart disease	1.168(1.128 to 1.210)	1.117(1.059 to 1.179)
Ischaemic heart disease ¹	1.129(1.125 to 1.134)	1.078(1.071 to 1.085)
Cerebrovascular disease ²	1.113(1.105 to 1.121)	1.092(1.081 to 1.103)
All cancers ³	1.088(1.085 to 1.091)	1.071(1.066 to 1.076)
Chronic Bronchitis ⁴	1.187(1.174 to 1.199)	1.177(1.158 to 1.195)
All causes	1.109(1.107 to 1.111)	1.081(1.077 to 1.084)

*Adjusted for crowding, density, social class and education.

¹ ICD 410-414, I20-25; ² ICD 430-438, I60-69; ³ I40-239, C00-D48; ⁴ 490-492; J40-44.

Figure 1: Association between levels of domestic air pollution (top) or overcrowding (bottom) and RHD mortality in the 78 local authority areas.

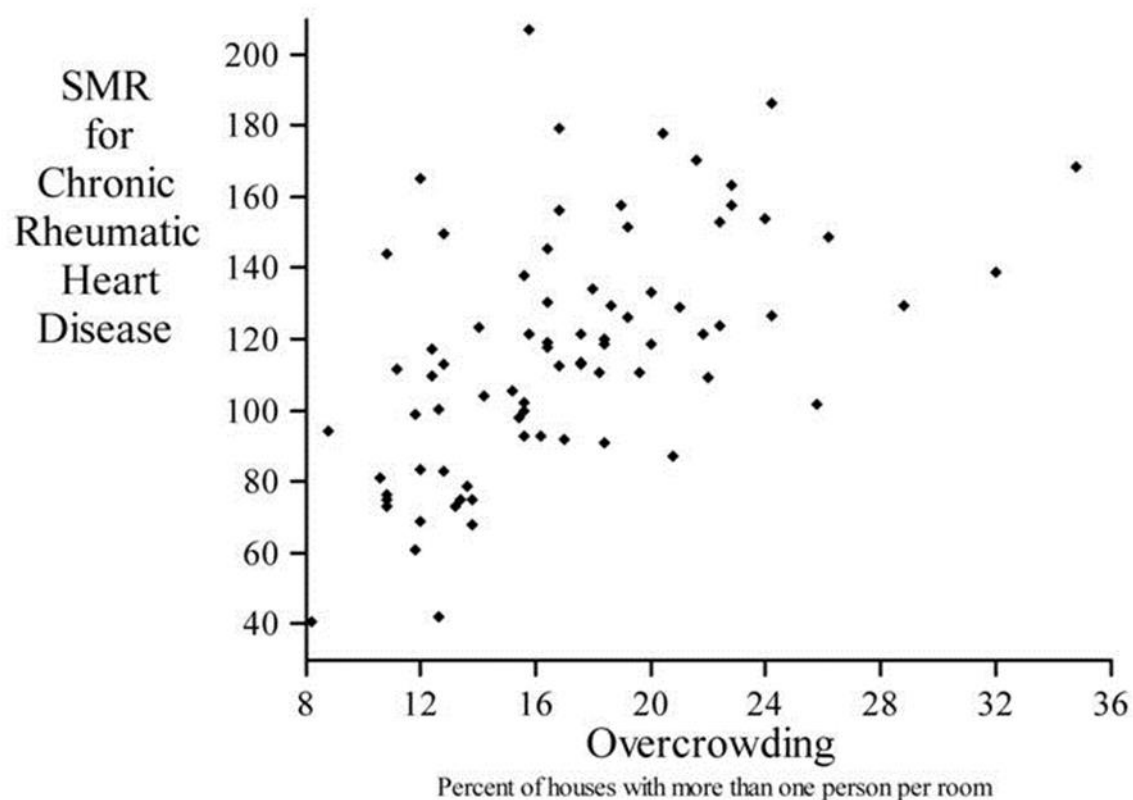
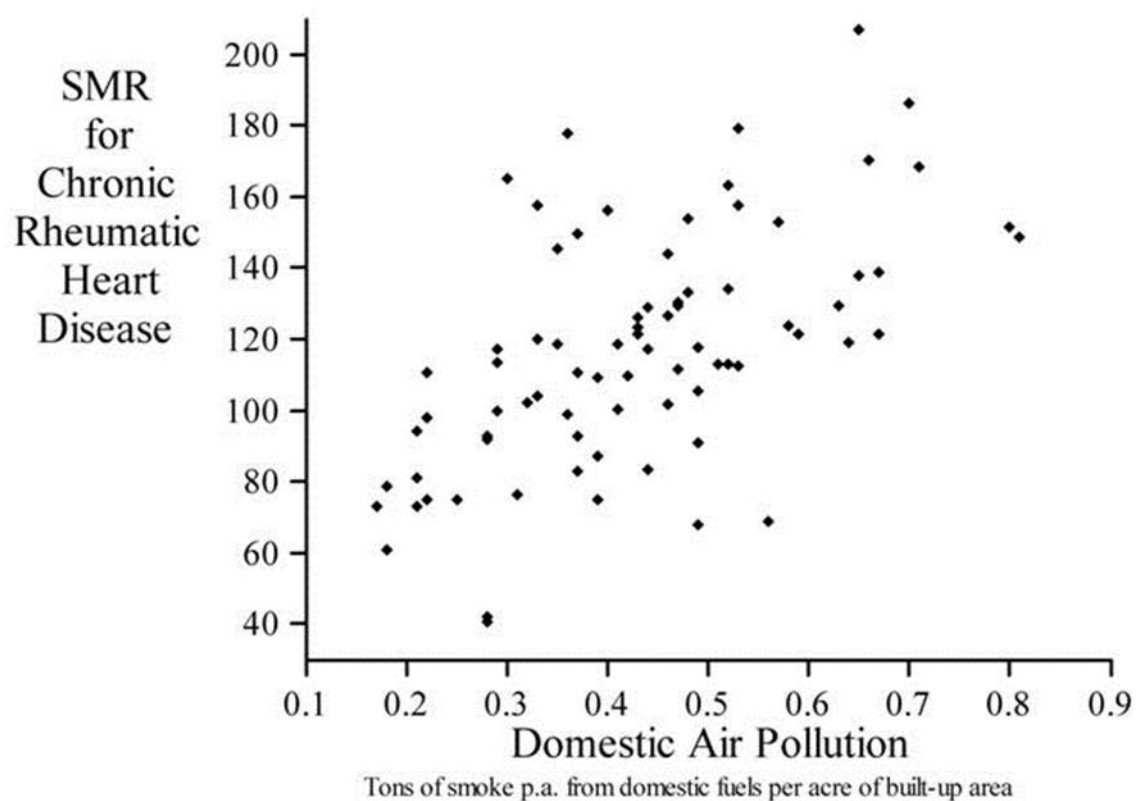
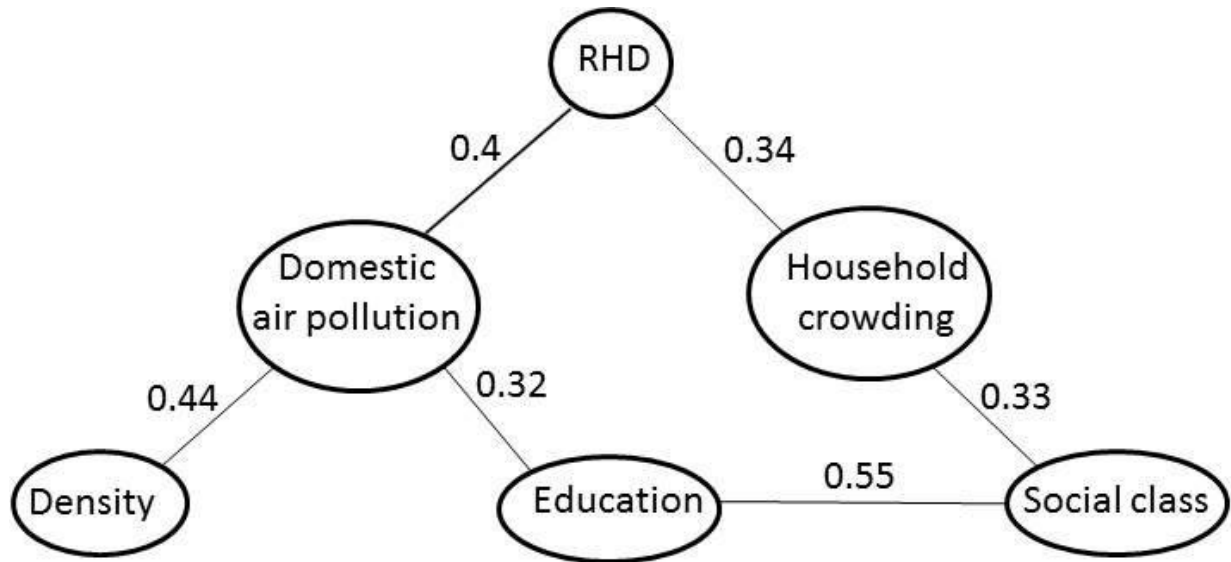


Figure 2: Conditional independence analysis. The figure shows the interrelationships and partial correlation coefficients between variables after controlling for all other variables.



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